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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,859	02/26/2002	Joseph Altin	EM436365176US	8566

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 03/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,859	ALTIN ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *16-20,22 and 36-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,21 and 23-35* is/are rejected.

7)☒ Claim(s) *2-15,23-26,28,29 and 32-35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the election requirement received on 1/7/05 has been entered. Claims 1-39 are pending in the instant application. Applicant's election with traverse of the following species: a) biological membranes which are not intact cells or liposomes; b) a target molecule which is VEGF; and c) encapsulated active material which is a cytotoxic drug. Claims 16-20, 22, and 36-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Claims 1-15, 21, and 23-35 are currently under examination. Please note that although claims 1-15, 21, 23-33, and 35 continue to read broadly on the genuses of biological and/or synthetic membranes or liposomes, targeting molecules, and encapsulated active materials, the claims have only been examined to the extent that they read on the elected species a), b), and c) as recited above. An action on the merits follows.

Election/Restriction

The applicant has traversed the election of species requirements, arguing in each case that the species share a specific technical feature. This is not agreed. Regarding intact cells, versus liposomes, versus synthetic membranes, versus biological membranes that are neither intact cells or liposomes, the applicant argues that they all share the special technical feature of being "membranes". Being a "membrane" is not a special technical feature. Membranes of many different forms were well known in the art and do not rise to the status of a "special technical feature". Further, as discussed in the election requirement, each species has substantially

different structural, chemical, physical, and functional properties from the others, such that the search for each in not overlapping. For example, a search for intact cells will not reveal art specific for liposomes.

In regards to the species of targeting molecule, the applicant again argues that the species share a special technical feature, in this case, the interaction with the metal chelating group in the amphiphilic molecule. Interaction with metal chelating group in the amphiphilic molecule is not a special technical feature that links each species. The use of histidine tags on proteins was extremely well known in the prior art, further VEGF is a protein with vastly different structural, physical and functional properties from co-stimulatory molecules such as B7 and CD40. Thus, the search for each species is not overlapping.

In regards to the species of encapsulated materials/agents/drugs, again no special technical feature exists which links all the species. The ability to be encapsulated within the membrane is not a special technical feature. The ability to encapsulate a variety of molecules in liposomes was well-established at the time of filing. Further, the individual species are vastly different in properties. The species include DNA, a cytotoxic drug, and proteins, all of which are distinctly different in chemical, physical, and functional properties such that a search for one species would be unrelated to a search from the other.

Regarding claims that read on the elected subject matter, please note that claims 16-20 are limited to preparing liposomes and do not encompass the elected species of biological membranes that are not intact cells or liposomes. Claim 22 and 36-39 are limited to target molecules which are either co-stimulatory molecules or molecules capable of modifying an immunological response, the elected species VEGF is neither a co-stimulatory molecule, nor a

molecule that modifies an immunological response. VEGF is an angiogenic protein. Thus, claims 16-20, 22, and 36-39 have been withdrawn.

Therefore, for reasons of record as discussed in detail above, the requirement is still deemed proper and is made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15, 21, and 23-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification fails to provide adequate written description for biological membranes which are not intact cells or liposomes. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations

using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). The applicant has not provided any description or reduction to practice of a single biological membrane which is not an intact cell or liposome which is capable of incorporating a chelator lipid and which is further capable of encapsulating a cytotoxic drug. Aside from a single reference on page 11 which states that a biological membrane can be any membranous or lipid-containing material obtained from biological systems such as cells, tissues, bacteria, viruses, or components thereof, the specification does not provide any description of any actual biological membrane that is not an intact cell or liposome. The specification's guidance and working examples are all directed to the use of intact cells and liposomes. Based on the applicant's specification, the skilled artisan cannot envision the detailed chemical structure of molecules and membranes which meet the claim requirements. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity

or simplicity of the method of isolation. See *Fiers v. Revel,* 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. Therefore, for the reasons outlined above, biological membranes which are not intact cells or liposomes are not adequately described by the specification as filed.

Claims 1-15, 21, and 23-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention as claimed.
The specification does not provide an enabling disclosure for making biological membranes which are not intact cells or liposomes into which have been incorporated amphiphilic lipids covalently attached to metal chelating groups. The specification broadly defines the invention using the terminology biological and/or synthetic membranes or liposomes. The specification provides specific guidance for biological membranes which are intact cells and for liposomes. The only teaching for biological membranes which are not intact cells or liposomes is found on page 11 which states that a biological membrane can be any membranous or lipid-containing material obtained from biological systems such as cells, tissues, bacteria, viruses, or components thereof. However, the specification neither provides examples of such membranous or lipid-containing material nor provides any guidance as to how to prepare such membranous or lipid-containing material from any of the listed sources such that the membranous or lipid-containing material is capable of incorporating a chelator lipid according to the instant methods and further capable of encapsulating or engrafting an active material such as a cytotoxic drug. In particular,

it is unclear how any component of a virus could be used a biological membrane in the instant invention. Viruses themselves do not produce a "membrane" or contain lipid material. It is well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). Furthermore, the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.
> Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997).

Therefore, in view of the lack of guidance concerning the actual physical and biological properties of any biological membrane which is not an intact cell or liposome, the lack of guidance for making or isolating such membranes, the lack of guidance provided for further modifying such membranes to include a chelator lipid and an encapsulated cytotoxic drug, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to practice the invention as claimed using biological membrane which is not an intact cell or liposome.

The specification further fails to provide an enabling disclosure for the therapeutic administration of a biological membrane which is not an intact cell or liposome, which comprises incorporated chelator lipid comprising a covalently attached metal binding group to which VEGF containing a polypeptide tag is bound, and which further includes an encapsulated cytotoxic drug. The specification also fails to an enabling disclosure for specifically targeting cells expressing VEGF receptor, *in vitro* or *in vivo*, using these particular membranes. The specification discloses that membranes prepared according to the claimed methods can be used to target specific cells *in vivo* in order to deliver therapeutic agents or to modify a biological response of the target cells. In particular, the specification discloses that attachment of VEGF to chelator lipid in the membrane and further encapsulation of cytotoxic drugs can be used to block the growth of new blood vessels need for the growth of tumors by targeting the cytotoxic drug to cells expressing VEGF receptor. As noted above, the specification fails to provide any guidance for making a biological membrane which is not an intact cell or liposome and which further includes a chelator lipid bound to VEGF and encapsulated cytotoxic drugs. The specification's working examples further fail to demonstrate that VEGF can be used to successfully target VEGF receptor expressing cells either *in vitro* or *in vivo,* and deliver any amount of encapsulated cytotoxic drug. Working example 4, proposes that VEGF can be engrafted to stealth liposomes by binding of his-tagged VEGF to the amphiphilic chelator lipid NTA-DTDA or NTA-PEG20000-PE. This example is prophetic and does not provide any actual evidence of successful engraftment of VEGF on stealth liposomes or any other membrane and further does not provide any evidence for targeted binding of the liposomes to vascular endothelial cells *in vitro* or *in vivo*, or for the inhibition of any vascular endothelial cell function following binding of the

liposome due to the activity of the encapsulated cytotoxic drug. At the time of filing, targeted delivery of liposomes, let alone other types of biological membranes, was considered unpredictable. In a recent review of Ligand-targeted liposomes, Forssen et al. concludes that while advances in lipid based drug delivery systems is encouraging, substantial hurdles remain to be overcome before these vehicles can be used to effectively delivery drugs to specific tissues or sites (Forssen et al. (1998) Adv. Drug Deliv. Rev., Vol. 29 (3), 249-271. In particular, Forssen et al. identifies problems with delivery due to immunogenicity, the selection of appropriate ligands with adequate selectivity and affinity for the target, the ability of the coupling method to correctly present the ligands to their binding site, and the ability of the delivery vehicles to maintain their entrapped contents until targeted binding occurs (Forssen et al., page 266). Thus, in view of the art-recognized unpredictability in the targeted delivery of liposomes and other vehicles to particular cells, the lack of guidance for making a biological membrane which is not an intact cell or liposome and which further includes a chelator lipid bound to VEGF and encapsulated cytotoxic drugs, the lack of working examples demonstrating the use of such biological membranes which are not intact cells or liposomes, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to make and use the invention as claimed..

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15, and 30-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is an independent claim which recites a method which comprises the step of "interacting a receptor domain which is covalently attached to a polypeptide tag with said membrane or liposomes for a time and under conditions sufficient for said polypeptide tag to attach to said membrane or liposomes via the outwardly facing metal chelating residues of said membrane or liposomes". Claims 2-15 depend on independent claim 1. However, dependent claim 4 recites the method of claim 1 wherein step (ii) includes interacting a "targeting molecule" with a "membranous structure" via the outwardly facing metal chelating residues of the membranous structure, "such that the receptor domains or targetable molecules" are capable of interacting with a specific type of cell. Claim 1 lack proper antecedent basis for the terms "the chelator lipid" and "the membranous structure" in step (i) of claim 4. Since the independent claim contains the limitation that it is a "receptor domain" that is interacted with the metal chelated group on the amphiphilic molecules, it is confusing when the dependent claim now recites interacting a "targeting molecule". The specification does not define a "receptor domain" per se, but receptors are a specific class of proteins with effector function whose activity is usually stimulated by the binding of a ligand to the receptor. A "targeting molecule" is not so limited and could potentially encompass any type of protein or other types of molecules including nucleotides or polysaccharides. The last few lines of step (ii) in claim 4 appear to recognize this distinction by referring to "the receptor domains or targetable molecules" in the alternative. Claim 5 further confuses the issue by reciting that the "targeting molecule" of claim

4 is a "receptor domain and/or other targeting molecule". Thus, the scope of the claims is indefinite in that it is unclear whether the applicant is trying to claim that both a receptor domain and a targeting molecule are bound though metal chelator interactions to the membrane or liposome, or whether the applicant intends the term "receptor domain" in claim 1 to read broadly on any targeting molecule. Please note as well that the elected species is VEGF. VEGF is a ligand for the VEGF receptor. Thus, while VEGF would be considered a "targeting molecule", it would not be considered a "receptor domain". Since the metes and bounds of claim 1 cannot be determined, it has been included in this examination since it is unclear whether it is intended to read on all targeting molecules or just on "receptor domains". However, should applicant indicate that claim 1 is in fact intended to be limited to "receptor domains", then this claim and all dependent claims will be withdrawn as being drawn to non-elected subject matter.

Claim 3 is further indefinite in that it does not appear to further limit claim 1. Claim 1 already recites that a proportion of the amphiphilic molecules in the membrane have been modified by a covalent attachment of a metal chelating group such that at least some of the metal chelating groups are oriented toward the outside surface of the membrane.

Claim 4 is further rejected for lacking proper antecedent basis for the terms "chelator lipid" and "membranous structure" and "metal binding residues". Claim 4 depends on claim1, however, claim 1 does not provide antecedent basis for the terms "the chelator lipid" or "the membranous structure" as recited in step (i) of claim 4, or for the term "metal chelating residues" as recited in step (ii) of claim 4.

Claim 9 is further indefinite in that it does not appear to further limit claim 1. Claim 1 already recites that a proportion of the amphiphilic molecules in the membrane have been modified by a covalent attachment of a metal chelating group.

Claims 30-35 are indefinite in their use of the words "anchoring or engrafting". The specification on page 24 states that the terms are interchangeable. Therefore, it is confusing why they are recited in the alternative. If they are intended to mean the same thing, then the use of both terms is redundant.

Claim 35 is further indefinite for the misuse of the term "when". The claim states, "A method according to claim 27 when used to enhance immunity to a specific tumor or disease". The clause starting with "when" is confusing and appears incomplete in this context.

Claim Objections

Claims 2-15, 22-26, 28-29, and 32-35 are objected to for the following informalities: all the listed claims are dependent claims which improperly start with the article "A". For dependent claims, the proper article is "The". Thus, all the dependent claims should begin with, "**The** method of claim .....". Appropriate correction is required.

The claims are free of the prior art of record in regards to the elected species: a) biological membranes which are not intact cells or liposomes; b) a target molecule which is VEGF; and c) encapsulated active material which is a cytotoxic drug. As noted in the beginning of this action, the claims have only been examined to the extent that they read on the elected

species. Since the claimed species are not allowable, see the rejection and objections to the claims above, search and examination of additional species is not required.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 9:30-6:00 EST. If the examiner is not available, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735. For all official communications, **the new technology center fax number is (571) 273-8300**. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

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PRIMARY EXAMINER